CHRONIC TOXICITY SUMMARY

CHLORINE DIOXIDE

(anthium dioxide; alcide; chlorine oxide; chlorine peroxide; chloryl radical; doxcide 50)

CAS Registry Number: 10049-04-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.6** µg/m^3 (0.2 ppb)
Critical effect(s)	Vascular congestion and peribronchiolar edema; hemorrhagic alveoli and congested capillaries in the lung in rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1994; CRC, 1994)

Description	Yellow to red liquid or gas
Molecular formula	ClO_2
Molecular weight	67.45 g/mol
Density	1.642 g/cm^3 @ 0°C (liquid)
Boiling point	9.9-11°C
Melting point	–59.5°C
Solubility	Soluble in water, alkaline and sulfuric acid solutions
Conversion factor	1 ppm = 2.76 mg/m^3

III. Major Uses or Sources

Chlorine dioxide is used directly as a bleaching agent for cellulose, textiles, flour, leather, oils, and beeswax. It is also used in the purification of water and as a bactericide and antiseptic (HSDB, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1136 pounds of chlorine dioxide (CARB, 2000).

IV. Effects of Human Exposures

Case reports of human occupational exposure to chlorine dioxide have shown that 19 ppm was fatal to one worker and 5 ppm was definitely irritating (Elkins, 1959). Seven out of 12 workers exposed regularly to chlorine dioxide at levels generally below 0.1 ppm (0.28 mg/m^3) reported symptoms of ocular and respiratory irritation leading to slight bronchitis (Gloemme and Lundgren, 1957). However, the authors ascribed the bronchitis to occasional acute excursions of

chlorine dioxide levels above 0.1 ppm due to technical problems such as equipment leakage. Concurrent exposure to chlorine and chlorine dioxide in pulp mill workers resulted in an increase in the reporting of subjective symptoms of irritation (Ferris *et al.*, 1967). In this study, the chlorine dioxide concentrations ranged from trace levels to 0.25 ppm (0.69 mg/m^3). No differences were found between these workers and controls by pulmonary function tests.

V. Effects of Animal Exposures

Eight rats (sex unspecified) were exposed for 5 hours/day, 5 days/week, for 2 months to 0 or 1 ppm (2.8 mg/m^3) chlorine dioxide (Paulet and Debrousses, 1972). The number of control animals was not specified. Microscopic evaluation of the lungs revealed vascular congestion and peribronchiolar edema in all animals exposed to chlorine dioxide. The subchronic LOAEL for respiratory effects was therefore 1 ppm (2.8 mg/m^3).

An earlier study by these researchers (Paulet and Debrousses, 1970) examined the effects of exposure to 2.5, 5, or 10 ppm chlorine dioxide for several hours/day for 30 days in rats and rabbits (n = 4-10 animals per group). Body weights, blood cell counts, and histopathological examination of the liver, lungs, and other tissues were measured in each group. At 10 ppm, nasal discharge, localized bronchopneumonia, and desquamated alveolar epithelium were observed. White and red blood cell counts were also increased with this exposure. Rats and rabbits exposed to 2.5 ppm for 7 hours/day for 30 days or for 4 hours/day for 45 days, respectively, showed significant respiratory effects, including hemorrhagic alveoli and inflammatory infiltration of the alveolar spaces.

Rats exposed to 5, 10, or 15 ppm (13.8, 27.6, or 41.4 mg/m^3) chlorine dioxide for 15 minutes, 2 or 4 times/day, for 1 month showed an increase in congested lungs, nasal discharge, and catarrhous lesions of the alveoli beginning at 10 ppm (Paulet and Debrousses, 1974). No significant changes in these parameters were seen at 5 ppm.

Dalhamn (1957) found that acute exposure to 260 ppm chlorine dioxide for 2 hours resulted in the death of 1 out of 4 rats. Five out of 5 rats died during exposures of 4 hours/day for 14 days. All exposed animals exhibited signs of respiratory distress and ocular discharge. No effects were seen in 5 rats exposed to 0.1 ppm for 5 hours/day, 7 days/week, for 10 weeks. Thus 0.1 ppm was a subchronic NOAEL.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Paulet and Debrousses (1970, 1972)
Study population	Wistar rats (8 per exposure concentration)
Exposure method	Discontinuous whole-body inhalation (0 or 1 ppm)
Critical effects	Vascular congestion; peribronchial edema in all animals; lung alveolar damage
LOAEL	1 ppm (2.8 mg/m^3)
NOAEL	Not observed
Exposure continuity	5 hours/day, 5 days/week
Exposure duration	2 months (2/24 = 8.3% of lifetime)
Average experimental exposure	0.15 ppm for LOAEL group (1 x 5/24 x 5/7)
Human equivalent concentration	0.23 ppm for LOAEL group (gas with thoracic respiratory effects, RGDR = 1.57 based on MV = 0.17 m^3, SA(Th) = 3,460 cm^2)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Inhalation reference exposure level	0.0002 ppm (0.2 ppb, 0.0006 mg/m^3, 0.6 μg/m^3)

The U.S. EPA (1995) based its RfC of 0.2 μg/m^3 on the same study but included a Modifying Factor (MF) of 3 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA. In addition OEHHA assigned uncertainty factors according to its peer-reviewed, approved methodology (OEHHA, 2000).

OEHHA earlier developed a chronic REL for chlorine of 0.2 μg/m^3 (0.08 ppb) based on hyperplasia in respiratory epithelium in female rats. Based on chemical reactivity, the REL for chlorine dioxide might be expected to be lower than that for chlorine. However, there are much less toxicologic data available for chlorine dioxide than for chlorine.

VII. Data Strengths and Limitations for Development of the REL

The REL for chlorine dioxide had uncertainties in all areas of concern. Thus the best available study was still limited by lack of multiple exposure concentrations, by the relatively short duration of exposures, and by the small number of animals examined. Adequate human health effects information is lacking, although it appears likely that the proposed REL would be protective of the effects reported in the single limited human study available. Other limitations were the lack of dose-response information and the lack of comprehensive data on multi-organ effects.

VIII. References

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